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Review

External beam radiation techniques for breast cancer in the new millennium: New challenging perspectives

Dodul Mondal *, **Daya Nand Sharma**

Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi 110029, India

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Abstract Radiation therapy in breast cancer has evolved dramatically over the past century. It has traveled a long path touching different milestones and taking unprecedented turns. At the end, a fine tune of clinical understanding, skill, technological advancement and translation of radiobiological understanding to clinical outcome has taken place. What all these have given is better survival with quality survivorship. It is thus prudent to understand breast irradiation in a new perspective suitable for the current millennium.

Contents

* Corresponding author.
E-mail address: dodulmondal@gmail.com (D. Mondal).

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Introduction

Breast cancer is one of the human cancers where therapeutic use of radiation has evolved dramatically over the past century. The journey is eventful which started with brachytherapy and still continuing in parallel to the most modern external beam radiation techniques. Slowly but steadily the use of fascinating sophisticated external beam radiation techniques is getting a foothold. Though parallel opposed tangent beams are considered standard technique till now, use of conformal radiotherapy with its full array including intensity modulation, image guidance, respiratory motion management and stereotaxy are in vogue and gaining pace. Whereas tangent beam is simple and easy to deliver, many of the new techniques are complex, time consuming, difficult to implement in large volume centers and not without risk of uncertainty. The resultant gain in therapeutic advantage is often questioned and associated risk of long term radiation damage from the newer techniques due to their inherent nature is promulgated as a major deterrent for their use.

It took a long time to establish the role of radiation as an essential component in adjuvant treatment of breast cancer. Radiation after BCS (Breast Conserving Surgery) for early as well as locally advanced tumor after neoadjuvant chemotherapy (NACT) is now considered as an integral part of BCT (Breast Conserving Therapy) whereas postmastectomy radiation (PMRT) to chest wall and or regional area is considered beneficial for a select group of high risk patients [1–5]. This group comprises of patients with four or more node positive diseases, extranodal extension of tumor, chest wall invasion by tumor, presence of tumor at the resection margin or having lymphovascular space invasion. The role of radiation in 1–3 positive nodes after mastectomy has always been an area of debate. However, a recent meta-analysis supports the use of radiation for this patient group also [6]. The meta-analysis conclusively supports beneficial role of postmastectomy radiation in patients with 1–3 positive nodes to reduce recurrence and breast cancer mortality.

In a very interesting multicenter study, patients with positive sentinel lymph node biopsy were randomized to receive either axillary radiation or underwent axillary dissection [62]. Patients receiving axillary radiation showed significantly less arm edema. This will definitely lead the way for nodal irradiation in future with improved quality of life.

A complex relationship exists between the tumor, its biology, host and treatment related parameters which ultimately dictates curability and thus giving rise to chance of a long term radiation induced morbidity in survivors. The choice of radiation technique is thus crucial to provide cure and mitigate the risk of long term complications. 2D planning is still the gold standard and as technology advanced, 3DCRT, IMRT with or without simultaneous integrated boost (SIB), arc therapy, Tomotherapy, stereotactic body radiotherapy (SBRT), and proton therapy are becoming more crucial for clinical use. Dosimetric studies are ample in literature and clinical use seems promising. Long term cardiac risk from the effect of radiation, particularly for left sided breast cancer is a concern for this favorable group of patients. New technologies are useful in reducing cardiac dose and thus can help in reducing long term cardiac morbidity and mortality. Another important breakthrough in the last two decades is establishment of hypofractionation as standard of care in many developed countries for whole breast radiation as part of BCT. For shortage of space, different dose fractionation schedule combined with radiation techniques will be discussed as a whole.

History of external beam radiotherapy in breast cancer

The journey of external beam radiation started in the last century with superficial X-rays and gradually moved on to high energy X-rays and photons including radionuclides like 60-Co (radioactive Cobalt) and 37-Cs (Cesium). The revolution in radiation oncology began post Second World War, with development of telecobalt followed by high energy linear accelerator in 1950 s. However it was only in 1960–1970 when linear accelerators came more into practice for therapeutic medical indications. This period is thus popularly called megavoltage era [7]. Changes were notably apparent in technical aspects of radiation, starting from manual surface marking based planning to adoption of computer and software. The advent of computed tomography (CT) scan in the field of radiation oncology further added to the sophistication with its robust use in simulation, segmentation, dose and inhomogeneity correction which all together brought a significant change toward individual patient based planning compared with earlier 2D standard planning techniques. Modern linear accelerators are also equipped with different imaging facilities which made patient positioning and treatment delivery precise thus providing the opportunity of reducing target volumes. All of these essentially lead to a theoretical dogma of less radiation induced morbidity. Again, for breast cancer, most of which are detected very early with increased patient awareness, thus giving rise to the issue of long term survivorship, the use of new technology must be well planned and thought to avoid morbid survival. With the ray of hope in sight, thus, toxicity reduction, notably skin toxicity, cardiac toxicity and ischemic heart disease, pulmonary toxicity and risk of pulmonary fibrosis seem to be manageable and reducible. This again, has been said with caution, given the young age of these modern techniques and lack of data to prophesize the future.

Modern planning and verification

Positioning and breathing motion

Conventionally, radiotherapy to breast is delivered in supine position with arms abducted beside head. Breast board is used for selected patients with significant chest wall angulation to make the anterior chest wall horizontal. Selected patients merit prone positioning to reduce heart and lung dose while keeping target coverage adequate. Evidences from both sides of the Atlantic prove that prone position is suitable particularly for large volume breasts after wide local excision of tumor [8–10,25]. However, caution should be exercised to take care of the CTV-PTV (Clinical Target Volume-Planning Target Volume) margin. Left sided small volume breast perhaps does not merit prone position treatment which actually may be detrimental [9].

Modern 3DCRT, IMRT, VMAT (Volumetric Modulated Arc therapy) or helical techniques give the freedom of multiple field placement from different angles and thus necessitating both arms to be placed above head in supine position. Using breast board, thermoplastic fixation device, head rest or other immobilization device like VacLok improve setup accuracy. When setup accuracy was compared between supine on Vac-Lok™ (CIVCO Medical Solutions, IA) versus prone on prone breast board positions, supine on VacLok immobilization device with headrest and arms over head showed better setup accuracy compared to the later technique in a series of patients treated with helical Tomotherapy [11]. The proposed dosimetric cardiac benefit from prone positioning may be overshadowed by the setup uncertainty and requirement for a larger CTV-PTV margin in this position.

Table 1 Description of different CTVs for radiation planning:

Structure	Contouring guideline
Whole breast CTV	Entire mammary gland (apparent CT glandular tissue) as defined in planning CT scan is contoured as whole breast CTV. The lumpectomy cavity should remain within this. Conventionally, the upper border remains at the insertion of second rib, lower border at the plane where glandular tissue disappears which corresponds to the inframammary fold, lateral border at mid axillary line excluding the latissimus dorsi muscle and medial border at sternocostal junction. Anteriorly the CTV goes up to skin. Posteriorly, it should exclude pectoralis muscles and ribs along with chest wall muscles. It is important to understand that the final PTV is created by editing off 4–5 mm thick strip of tissue underneath the skin anteriorly to spare the skin from high dose and to create dose build-up region. It must be kept in mind that, clinical and CT definition of structures should be complimentary to each other
Lumpectomy GTV	Defined as the surgical bed, as determined by surgical clips placed in the lumpectomy cavity during surgery. Where clips cannot be placed due to logistic reasons, lumpectomy cavity or seroma cavity formed after surgery as seen in planning CT scan should be contoured as the tumor cavity or lumpectomy cavity
Chest wall CTV	In contrast to whole breast CTV, chest wall CTV includes skin, pectoralis muscles, intercostal muscles and ribs as part of it. Superior border remains at the caudal end of head of clavicle. Inferior border lies at the plane of loss of apparent CT glandular tissue of opposite breast, medial border lies at sternocostal junction and lateral border lies at mid axillary line excluding latissimus dorsi muscle. The costo-pleural interface serves as the posterior border. Though it is wise to include mastectomy scar within CTV, it is not always necessary for scars extending beyond midline
Nodal CTV	Interested readers may follow the link provided in the reference for detailed information. It is beyond the scope of this article to describe this

Respiratory gating in the inspiratory phase or Deep Inspiration Breath Hold (DIBH) technique have been found effective in reducing irradiated volume of the heart. The idea is to keep heart out of radiation field as much as possible which is crucial in treating left sided breast cancer. With inspiratory gating or DIBH, it is possible to reduce V_{50} of heart significantly [12]. This is expected to translate in clinical benefit in terms of reduced long term cardiac morbidity and mortality. The overall effect of respiratory gating is thus promising in modern day breast radiation [13].

Unlike the fluoroscopy guided simulation and manual dose calculation of previous age, modern day radiotherapy planning software is capable of visualizing target and organs at risk (OAR) in three dimension. Options like autosegmentation and various other contouring tools have made target delineation process easier compared to earlier time. Visualization of the tumor cavity and or clips at the cavity margins, provide better cavity delineation and also guides selection of appropriate electron energy and depth when boost is planned with electron [14–16]. Availability of RTOG (Radiation Therapy Oncology Group) contouring guideline [17] has made delineation of various structures more systematic, reproducible and error free. The presence of soft tissue, bone, cartilage, lung tissues and air cavities in radiation pathway having different electron densities and thus beam attenuation, give rise to chance of uncertainties. More recently developed software also provides the opportunity to correct different tissue inhomogeneities and calculate dose and monitor units more precisely [7].

Contouring of normal structure and target volume

Earlier, borders of intact breast were used to be defined clinically depending upon standard anatomical landmarks and clinical extent of palpable breast tissue. The advent of CT scanners now gave the facility to see the cavity and or the seroma within it, surgical clips at the cavity margins, breast parenchyma and non-breast fatty tissues. Whereas, the following recommendations (Table 1) can be used for delineation of different CTVs, interested readers are requested to follow the link for more detailed information [17].

Treatment verification

Modern day linear accelerators are equipped with various gantry mounted imaging devices for setup verification and image guidance. Most of these treatment verification systems are X-ray based. A conventional X-ray source with opposing flat panel detector is mounted over the gantry. This gives the benefit of generating kilovoltage Cone Beam CT (kVCBCT) with high image resolution. The megavoltage X-ray source of the linear accelerators can also be used with an opposing flat panel detector (EPID) for image verification purpose. This MVCBCT has the advantage of using same source of radiation for treatment and imaging, thus avoiding uncertainty of artifact and needs to extrapolate attenuation coefficient, albeit with a poor quality image compared to kVCBCT. Three dimensional images are acquired with rotation of the X-ray source around the target and further reconstruction. Use of respiratory gating technology has become more common for thoracic radiation to make treatment delivery further precise. Four dimensional CT scan and Real Time Tumor Tracking are few examples of this method. These technologies have not only revolutionized radiation delivery precision, but also given the chance to reduce the CTV-PTV margin and effectively reduced normal tissue toxicity. Additional radiation dose from frequent X-ray based imaging has been a concern of second malignancy [18] thus giving way to MR based image guidance systems.

Incorporation of all these methods has brought into practice newer radiation delivery technologies. This article briefly describes the current advances pertaining to external beam radiation therapy techniques in breast cancer.

New techniques

Three dimensional conformal radiotherapy (3D-CRT)

With the availability of better computerized treatment planning system, it has become easier to generate multiple plans for a given patient. One of the most serious concerns of breast radiotherapy is long term cardiac toxicity. The risk of long term major cardiac complications are linearly increased with mean heart dose and an estimated risk of 7.4% was found with every 1 Gy mean dose increment to the heart [19]. In a recent analysis of a cohort of cancer patients from Sweden, treated between 1970 and 2003, a detailed angiographic mapping of stenosed cardiac vessels was done with respect to radiation portals. This study has shown significant association between radiation and cardiac stenosis location [54]. In a dosimetric study from India by Roy et al. [55], dose to left anterior descending coronary artery (LADCA) and left circumflex coronary artery (LCx) was analyzed for early breast cancer patients treated either with conservative surgery or mastectomy. Data were analyzed to see any difference with left or right sided tumor. The authors demonstrated an increased dose to LADCA irrespective of the nature of surgery (conservation/mastectomy). These along with numerous other studies have demonstrated risk of increased cardiac dose leading to perfusion defect and risk of long term cardiac morbidity and mortality [56,57]. Over the years conformal radiotherapy has given an edge over conventional radiotherapy to minimize cardiac dose. Various combination of gantry angles, number of fields including field in field (FiF), beam weightage, wedge pair combination, multi leaf collimator (MLC) positioning and different energy combination, are some of the effective ways to reduce heart dose with 3DCRT [13,20–24]. With effective implementation of cardiac protective radiation techniques, dose to left side of heart has been reduced compared to earlier time [58].

With conventional 2D tangential beam technique, covering entire breast parenchyma sometimes becomes impossible. This problem can be overcome using conformal technique. To avoid inadequate target coverage due to respiratory motion, anterior border of field is usually placed 1.5–2 cm anterior to the skin to accommodate the breast during its respiratory excursion. Mechanical block of heart and lung is possible by MLC positioning reducing cardiac and lung volume within radiation beam. 3D plan was found to be dosimetrically superior compared to standard 2D plan in a study by Aref et al. in 85 patients with intact breast [25]. Multifield conformal radiotherapy has the risk of greater volume of normal tissue receiving low dose of radiation which is of particular concern for second malignancy.

The recent surge seen with use of 3DCRT is attributed to more number of patients being treated with accelerated partial breast irradiation (APBI). Published data have shown APBI as a feasible technique with local control, toxicity and cosmesis comparable to standard APBI techniques like interstitial implant. In fact, the rise of 3DCRT followed after one of the early studies from William Beaumont Hospital showed that limited field radiation after breast conservation is comparable in terms of local control [26]. Even with prone position APBI, 3DCRT was feasible and provided comparable tumor control with additional benefit of heart and lung being completely spared out of the radiation field [27–29]. Multiple other studies have also shown acceptable acute and late toxicity with comparable tumor control using 3DCRT APBI. However, one study has also reported increased late toxicity and poor cosmesis from 3DCRT APBI [30]. When compared with proton beam APBI, in a phase1 study, 3DCRT APBI showed comparable local control with better long term cosmetic outcome [31].

Intensity modulated radiotherapy (IMRT)

Since inception, IMRT has been promising in achieving excellent dose distribution and organ sparing. It is thus nothing surprising that IMRT would be tried for breast cancer as well. Due to the fact that the intensity of the beam can be varied with practically any available angle to direct the beam along with the facility to either treat with fixed field or dynamic technique, IMRT is definitely a game changer in modern day radiotherapy practice. Dosimetric studies have successfully documented superiority of tangent IMRT compared to 2D conventional planning or 3DCRT in providing excellent target coverage, better OAR sparing but at the cost of increased low dose normal tissue volume, giving rise to future second malignancy risk [32–34]. When these dosimetric approaches were clinically tested, IMRT showed comparable local control with less skin toxicity and better cosmesis [35–37]. Significant improvement was noticed in reducing moist dermatitis in these trials. Breast size was found to be independently associated with risk of moist dermatitis. Patients having smaller breast volume and large breast volume were found to have less skin toxicity compared with medium volume breast, when treated with IMRT [35,36]. However, the Royal Marsden study excluded patients with breast volume < 500 cc from receiving IMRT considering fairly homogenous dose distribution with standard 2D technique [37]. In another dosimetric study in postmastectomy patients, tangent IMRT showed better sparing of lung and heart compared with tangent 3DCRT [38].

In a large series of single institute experience with inversely planned IMRT, Yang and his colleagues have shown good locoregional control, acute toxicity and acceptable cosmesis in patients treated with inversely planned IMRT for whole breast and locoregional irradiation [39]. Large PTV volume (> 520 cc) was significantly associated with more acute skin toxicity.

One of the interesting recent developments is incorporation of simultaneous integrated boost after BCS. The rationale behind was requirement of additional boost after whole breast radiation in many patients. The dosimetric advantage was enormous with SIB. First of all, it gave the opportunity to look at the OAR tolerance achievement at the beginning of the treatment and thus avoiding any future uncertainty. Secondly, the radiobiology of breast tumor and normal surrounding tissue facilitated hypofractionated treatment, which SIB can achieve more easily than a sequential boost plan. Thirdly, the effective duration of treatment could be made shorter compared to prolonged fractionated treatment.

Evidence showing advantage of hypofractionation in providing adequate locoregional tumor control with comparable cosmesis helped establishing this simultaneous boost approach [40–44]. Arc therapy including volumetric modulated arc therapy (VMAT®) and Rapid Arc® have been also promising with few clinical studies showing its feasibility and acceptability in implementation, tumor control and acute toxicity with good to acceptable cosmesis in most patients.[45,46] The RTOG 1005 study will be a giant foot forward in this regard once the clinical outcome data are published.

Another interesting recent development related with IMRT for breast cancer is resurgence of internal mammary nodal (IMN) radiation. With survival advantage in sight, studies are ongoing to evaluate feasibility of cardiac sparing IMN radiation and its clinical benefit in postmastectomy and whole breast radiation [47–50].

Caution must be exercised before implementing this technique so as to avoid unnecessary and unprecedented high dose to normal tissues in order to achieve target coverage. The entire idea of IMRT can backfire due to its "double edged sword" nature. Rigorous quality assurance, training and expertize in different aspects of radiation planning starting from immobilization to treatment verification and toxicity evaluation are crucial.

One less discussed issue about IMRT in breast cancer is dose received by lung with resulting toxicity. Clinical data are sparse and immature to comment on the possible late pulmonary complication developing from a large volume of lung receiving low dose radiation from inversely planned multifield IMRT or arc therapy. The advent of newer techniques every other year and replacement of the older one is definitely a deterrent in assessing the late pulmonary effects of breast radiation with a particular technique which requires many years of systematic follow up.

Stereotactic body radiotherapy (SBRT)

Not very surprisingly, SBRT is also getting its way in field of modern breast radiation oncology. A high dose per fraction radiation delivered in either single fraction or multiple fractions before conservation surgery for a strictly selective group of patients showed promising results [51,52]. Like other preoperative approach, this has also its advantages of visualizing intact tumor before it is surgically disturbed, smaller target volume compared with postoperative target, tumor having intact blood supply and to add to it, shorter time due to large dose per fraction. The data of SBRT are not mature enough and not validated in a large prospective study with long term follow up in terms of long term disease control and cosmesis. The limited application of this technique within the boundary of APBI is promising though.

Proton beam therapy

Clinical use of proton beam external radiotherapy in breast cancer has been on the rise since the last decade. The physical property of proton beam with its Bragg peak effect gives the advantage of excellent target coverage with OAR sparing to a great extent. Depending on the depth and thickness of the PTV, modulation of proton beam is also possible to generate adequate dose distribution. Among the different algorithms, the pencil beam scanning (PBS) proton therapy (PT) provides best conformity to the tumor. Multiple small pencil beams cover the tumor in a three dimensional plane. This seems clinically useful with intensity modulation providing greater skin sparing and adequate coverage of the tumor cavity, while reducing underlying critical OAR dose Intensity Modulated Proton therapy (IMPT) has thus become a new way to treat breast cancer and being implemented both in early breast cancer and postmastectomy radiotherapy. Majority of the dosimetric work along with few early clinical studies have been evaluating its role in APBI and chest wall radiotherapy. Cardiac sparing and skin sparing is excellent in these initial reports. In a study by Wang and his colleagues, [53] proton beam APBI was found to generate significantly better plan when compared to photon beam 3DCRT. Absolute reduction of the mean of V100, V90, V75, V50, and V20 for normal breast using Passive Scattering Proton Beam (PSPB) was 3.4%, 8.6%, 11.8%, 17.9%, and 23.6%, respectively. For breast skin, with the similarV90 as 3DCRT photons, the proton plan significantly reduced V75, V50, V30, and V10. Cardiac and lung doses were also reduced significantly with proton beam.

The same dosimetric advantage was not seen in another proton beam clinical study [31]. 98 prospective patients with stage I breast cancer were treated either with photon beam 3DCRT APBI or proton Beam Therapy APBI (PBT APBI). At 7 years, evaluable patients showed comparable tumor control with higher rates of long-term telangiectasia, skin color changes, and other skin toxicities in PBT APBI arm.

The effectiveness of PBS-PT is seen in selective pediatric intracranial tumor, adult pelvic tumor and post mastectomy radiotherapy [59–61]. The recently published data from Massachusetts General Hospital has also proven dosimetric advantage of PBS-PT for postmastectomy radiotherapy using PBS-PT [61]. Skin dose, cardiac dose and nodal coverage were more favorable in patients treated with scanning Proton therapy compared with passive scattering (PS) proton beam.

It will require more time for the proton beam to generate robust evidence for its routine clinical use in breast radiotherapy considering available low cost technologies being almost equal to it in clinical outcome.

Conclusion

External beam radiation in breast cancer has reached a new horizon. Once dominated by brachytherapy, early stage breast cancer has also observing increased utilization of newer EBRT techniques. Availability and progress in technology related to imaging, treatment delivery and verification have made this a rapidly changing subject in the last decade. Whereas the most important end point, tumor control and survival, has remained essentially the same, there are increased benefits in terms of better cosmesis, reduced acute and late radiation morbidity, reduced long term cardiac morbidity, and reduced patient suffering due to short duration of treatment. All these are perhaps leading this commonest cancer to have a better survivorship.

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Conflict of interest statement

None.

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